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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/777,856	02/07/2001	Ami Aronheim	01/21605	3362

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Martin D. Moynihan
PRTSI, Inc.
P. O. Box 16446
Arlington, VA 22215

EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/777,856	ARONHEIM ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/9/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-11,15-19,24-29,33-35 and 50-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6-11,15-19,24-29,33-35 and 50-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 June 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to an amendment filed 7/9/07. Claims 1, 2, 6-11, 15-19, 24-29, 33-35 and 50-52 are pending in the instant action.

Claim Objections

Claims 7 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. According to the specification, Ras signaling is inactivated in the recited cells at restrictive temperatures by loss of Cdc25, which results in growth suppression. Complementation of the mutant Ras phenotype inherently results in complementation of the phenotype associated with the Ras mutant (growth suppression) as well as Ras signaling.

Claim 1, 9, 18 and 27 are objected to because of the following informalities: claim 1, line 5, claim 9, line 5, claim 18, line 8 and claim 27, line 8 recite that the bait polypeptide being capable of interacting with *a* plasmalemma of the cell whereas it would be more grammatically correct to recite --the plasmalemma-- of the cell.

Claims 1, 9, 18 and 27 recite throughout "being capable" or "being from" which would be grammatically clearer if recited simply as --capable-- or --from--.

Claims 18 and 27 recite in section (i) a series of requirements of the first polynucleotide such as operable linkage to a first inducible promoter and encoding a polypeptide wherein the first polypeptide is fused to a second polypeptide. However, (i) would be clearer if recited as --a first polynucleotide from a library of polynucleotides wherein each polynucleotide wherein each polynucleotide of said library of polynucleotides is operably linked to a first inducible promoter,

said first polynucleotide encodes a first polypeptide capable of interacting with the plasmalemma of said cells fused to a second polypeptide-- as the claim does not clearly set forth all of the components of the first polynucleotide.

Claim 18(b) recites "identifying said Ras signaling in said cells of said plurality of cells". However, for accuracy and consistency, the recitation should be amended to recite -- identifying said Ras signaling in each of the cells of said plurality of cells--.

Claims 52 and 53 recite that Ras signaling is detected under "said different inductive conditions". If the claims intend that only induction from the second promoter occurs in claim 52 and 53 it would be remedial to recite that said second inducible promoter is induced to resulting expression of said second polypeptide and compared to non-inductive conditions. However, recitation that the promoters are induced by different inductive conditions and that these different inductive conditions are used suggests that both promoters are activated in claims 52 and 53. Yet, claims 52 and 53 are limited to activation of only the second promoter.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 8 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These are new rejections.**

Claim 8 recites the limitation "said second polypeptide being" in line 7. There is insufficient antecedent basis for this limitation in the claims. It appears that the limitation should be –second polynucleotide--.

Claim 19 is vague and indefinite in that the metes and bounds isolating a "polynucleotide encoding said second polypeptide" are unclear. The polynucleotide of claim 18 encodes a first polypeptide and while the claim does not recite that that polynucleotide encodes the second polypeptide, it appears that it does as a fusion. Even if the polynucleotide were clarified to encode the first and second polypeptide, it is not clear how a polynucleotide encoding the second can be isolated without also referencing that the first polypeptide is also encoded by the sequence.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6-11, 15-19, 24-29, 33-35 and 50-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying interactions between polypeptides comprising expressing in a cell lacking active Ras protein or an upstream regulator of Ras, a first polynucleotide operable linked to an inducible promoter and encoding a polypeptide or a fusion polypeptide that interacts with the plasmalemma of the cell and a second polynucleotide encoding a polypeptide fused to a Ras mutant that is incapable of self-targeting to the plasmalemma membrane of the cell (alternatively, the first and/or second polynucleotides can be part of a library of polynucleotides) wherein in the case that "said cell lacking Ras signaling is a yeast cell exhibiting a mutant Ras phenotype characterized by growth suppression under non-permissive conditions" the cell is a yeast cell comprising a temperature sensitive mutation in Ras or CDC25 wherein under restrictive temperatures Ras signaling is inhibited and thus cell growth, does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat.

App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

The instant claims are drawn to a method for identifying protein-protein interactions by use of a modified Ras Recruitment system. Specifically, the invention minimizes false positives by design of a system comprising 1) an inducible promoter driving expression of a bait peptide or a fusion peptide that binds to the plasmalemma of the cell and 2) a second polynucleotide encoding a prey peptide fused to a Ras mutant that is incapable of self-targeting to the plasmalemma. Expression of the second polynucleotide was found to result in 5% of transformants to give a false positive signal in the absence of bait peptide. Hence, by design of a bait peptide under control of an inducible promoter, the invention avoids isolation of the false positives. Those clones in the absence of induction of the first polynucleotide are false positives. However, the claims are quite broad in that the claims recite use of *any* cell lacking Ras signaling in which the cell expresses *any* "cytoplasmic Ras mutant, said cytoplasmic Ras mutant being capable of said Ras signaling if mobilized to said plasmalemma of said cell". The combination of the two elements as broadly claimed results in a high degree of predictability of the instant invention.

The MPEP teaches, "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). By recitation of the broad genus of cell/mutant combinations, the claims

lack a structural functional relationship such that a person of skill in the art could identify those elements critical to the instant method. The claims require that the signaling be lacking such that it can be complemented. For such to occur, the combination would have to be 1) an inactive Ras that is replaced by the transiently expressed Ras mutant or 2) an inactive regulator of Ras in which the Ras signaling pathway is inactive and complemented by a constitutive Ras mutant. Examples of either are present in related inventions in the art. However, as broadly recited, the Ras signaling that is lacking in the cell can be a pathway that is not complemented by reintroduction of a Ras mutant as Ras signaling is a result of a myriad of pathways both that input and output through Ras. For example a Ras mutant cannot restore a defect originating in MAPK or Raf signaling. Hence, the defect in the cell must either be a regulator of Ras or Ras itself. Secondly, the claims are broadly drawn to any Ras cytoplasmic mutant whereas use of any Ras cytoplasmic mutant does not guarantee that the defect in Ras signaling is restored even if the defect is properly limited to a regulator of Ras or to Ras itself (see Johnson et al for example). Rather, the Ras mutant must be a mutant that is not capable of self-targeting and that complements the defect in Ras or Ras activation. Hence, the cell/mutant combination cannot be as broadly recited.

Several claims recite use of "a yeast cell exhibiting a mutant Ras phenotype characterized by growth suppression under non-permissive conditions". The specification teaches that cells usable in the instant method are an *S. cerevisiae* strain, Cdc25-2, which has a mutation in the Cdc25 gene. Cdc25 encodes an upstream regulator of Ras and the mutation renders Cdc25 temperature sensitive, with nearly wild-type activity at 25°C. Growth at restrictive temperature can be restored by expression of a membrane-associated constitutively active Ras mutant.

Hence, Ras signaling is inactivated in the cells at restrictive temperatures by loss of Cdc25, which results in growth suppression. Complementation of the mutant Ras phenotype is complementation of growth suppression and this inherently occurs through Ras complementation. The art teaches use of this strain of yeast cells in several variations of Ras recruitment methods. However, the cell as recited encompasses broadly any number of Ras mutations that may not be usable in the instant claims for reasons provided above. Rather, the cells must be Ras mutant cells that lack Ras signaling by loss of Ras or an activator or Ras and then consequently complemented by a transfected Ras mutant.

The invention recites use of a broad group of cell/mutant combinations. Given the lack of adequate working examples and the lack of guidance provided by applicants for the broadly recited claims, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 6-11 and 15-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Aronheim et al (Current Biology, 1998, pages 1125-1128; see entire document) as evidenced by Invitrogen pYES map and Broder et al (Current Biology, 1998, pages 1125-1128). **This is a new rejection.**

Aronheim et al teach a method of identifying interactions between polypeptides comprising use of cdc25-2 yeast strain, which cells lacks Ras signaling (see figure 2). The cells were transfected with a first polynucleotide comprising an inducible promoter as evidenced by Invitrogen plasmid map and Chp polynucleotide fused to v-Src myristoylation sequences (see e.g. abstract). As evidenced by Chenette et al, Chp is a membrane protein (see e.g. page 3108, col 1). The cells were transfected with a second polynucleotide comprising a fusion of a second polynucleotide and pRasL61 an expression vector comprising a Ras mutant. Cells were grown under inductive conditions to induce the gal1 promoter and non-inductive conditions (see figure 2 and elucidation of the method in Broder et al , page 1122). It is the difference between the two that indicates an interaction between a first and second polypeptide. Following growth of cells under inductive and non-inductive conditions, a clone expressing CBP in complex with b-catenin was identified upon isolation of a subset of cells (see e.g. page 251, column 1, paragraph 4). The cdc25-2 cells are growth suppressive under non-permissive temperatures. This phenotype is corrected by translocation of the Ras mutant to the plasmalemma. The first polynucleotide was isolated from a library of polynucleotides and absent evidence to the contrary, the second polynucleotide could have been isolated from a library of potential clones.

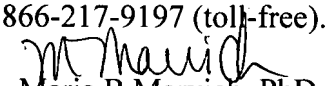
Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Maria B Marvich, PhD
Examiner
Art Unit 1633